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Editorial

Therapeutic potentials of catalase: Mechanisms, applications, and future perspectives

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Catalase, an enzyme ubiquitous in living organisms, plays a pivotal role in mitigating oxidative stress by catalyzing the decomposition of hydrogen peroxide (H_2O_2) into water and oxygen. Mechanistically, this action prevents the accumulation of reactive oxygen species (ROS) and consequent oxidative damage to cells and tissues. Understanding the molecular mechanisms underlying catalase activity, exploring its therapeutic applications across diverse disease contexts, addressing challenges in catalase-based therapies, and advancing novel strategies for enhanced efficacy are essential steps toward harnessing its full therapeutic potentials. In the medical realm, catalase shows promise for treating oxidative stress-related diseases such as neurodegenerative disorders, cardiovascular diseases, and inflammatory conditions. This article explores the therapeutic potentials of catalase, focusing on its mechanisms, applications, and future perspectives.

Catalase, an enzyme present in nearly all living organisms exposed to oxygen, plays a crucial role in protecting cells from the harmful effects of ROS. Its significance in cellular physiology extends beyond mere protection; catalase influences various metabolic processes and is increasingly recognized as a potential therapeutic target for a range of diseases.[1-3] Catalase, classified as a peroxidase enzyme, is primarily found in the peroxisomes of eukaryotic cells and in some bacteria.[4,5] Structurally, it consists of four subunits, each containing a heme group essential for its catalytic activity. The enzyme catalyzes the decomposition of H_2O_2 into H_2O and molecular oxygen (O_2). This reaction is vital as hydrogen peroxide, a byproduct of various cellular processes including aerobic respiration, can be toxic if allowed to accumulate.[5,6] Catalase efficiently mitigates this toxicity by rapidly breaking down hydrogen peroxide into harmless substances. As it plays an important role in cellular physiology such as it acts as one of the primary defense mechanisms against ROS by efficiently converting hydrogen peroxide, a precursor to highly reactive hydroxyl radicals, into water and oxygen, thus preventing oxidative stress.[6] Catalase, along with other antioxidant enzymes, helps to maintain this balance, thereby protecting cells from oxidative damage associated with aging, inflammation, and various diseases, including cancer, neurodegenerative disorders, and cardiovascular diseases.[7,8] Catalase also plays a role in regulating cellular signaling pathways involved in growth, proliferation, and apoptosis. By modulating the levels of hydrogen peroxide, catalase influences redox-sensitive signaling molecules such as protein kinases and transcription factors, thereby impacting cellular responses to environmental cues and stressors.[9] Beyond its role in ROS detoxification, catalase is implicated in various metabolic processes. Studies have shown that catalase deficiency or dysfunction can lead to metabolic dysregulation, including impaired glucose metabolism and lipid accumulation, highlighting its broader involvement in cellular homeostasis.[10,11] Rationale for investigating catalase as a therapeutic agent, the multifaceted role of catalase in cellular physiology underscores its potential as a therapeutic target for various diseases. Several factors contribute to the rationale for investigating catalase-based therapies such as oxidative stress-related disorders. Given its central role in ROS detoxification, catalase holds promise as a therapeutic agent for conditions characterized by oxidative stress, including neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease), cardiovascular diseases (e.g., atherosclerosis and ischemia-reperfusion injury), and metabolic disorders (e.g., diabetes and obesity).[1-3,5,11] Anti-inflammatory properties and catalase's ability to mitigate oxidative stress also translate into anti-inflammatory effects. By reducing the production of ROS-derived inflammatory mediators, catalase has the potential to alleviate inflammation associated with various chronic conditions, such as arthritis, inflammatory bowel disease, and asthma.[12,13] Neuroprotective effects, the brain is particularly vulnerable to oxidative damage due to its high metabolic rate and abundant lipid content. Catalase-based therapies show promise for neuroprotection by preserving neuronal integrity and function, thereby offering potential avenues for treating or preventing neurodegenerative disorders.[14] Cardiovascular health and oxidative stress play a crucial role in the pathogenesis of cardiovascular diseases, including atherosclerosis, hypertension, and myocardial infarction.[15] Catalase-based interventions may help to mitigate oxidative damage to the cardiovascular system,

thereby reducing the risk of adverse cardiovascular events and improving overall heart health.[16] Potential for gene therapy, advances in gene therapy techniques offer new opportunities for delivering catalase genes or enhancing endogenous catalase expression in target tissues. Gene-based approaches hold promise for precise and long-lasting interventions, particularly in conditions where catalase deficiency or dysfunction contributes to disease pathology.[14,16]

Regulation of catalase expression and activity, the expression and activity of catalase are tightly regulated at multiple levels, ensuring precise control over cellular redox homeostasis and oxidative stress response. Transcriptional regulation represents a primary mode of controlling catalase abundance, with numerous transcription factors adopting its expression in response to environmental cues.[17] The redox-sensitive transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a master regulator of antioxidant gene expression, including catalase, under conditions of oxidative stress.[18] On activation, Nrf2 translocates to the nucleus and binds to antioxidant response elements within the promoter region of target genes, augmenting their transcriptional output. In addition to transcriptional regulation, post-translational modifications modulate catalase activity in response to changing cellular conditions. Phosphorylation, acetylation, and ubiquitination represent prominent modes of enzymatic regulation and fine-tuning catalase activity in a context-dependent manner.[19] Furthermore, the subcellular localization of catalase contributes to its regulatory repertoire, with dynamic shuttling between cytosolic and peroxisomal compartments influencing its accessibility to substrates and regulatory factors. Perturbations in subcellular localization can profoundly impact catalase function, altering its efficacy in mitigating oxidative stress-induced damage.[17-19] Emerging evidence also implicates non-coding RNAs, including microRNAs and long non-coding RNAs, in the post-transcriptional regulation of catalase expression. These regulatory RNAs fine-tune catalase abundance by modulating mRNA stability and translation efficiency, adding another layer of complexity to the regulatory landscape governing catalase activity.[20,21]

Unraveling the crucial role of catalase in oxidative stress-related diseases, among the plethora of antioxidant enzymes, catalase shines as a sentinel, playing a pivotal role in mitigating oxidative damage and preserving cellular homeostasis. Now, it is well established that the multifaceted involvement of catalase in oxidative stress-related diseases, spanning cardiovascular disorders, neurodegenerative diseases, diabetes mellitus, cancer, and aging.[1-5] Catalase, abundant within cardiac tissue, stands as a frontline defender against oxidative insult, safeguarding cardiomyocytes from ROS-induced damage.[22] In conditions such as ischemia-reperfusion injury, characterized by transient oxygen deprivation followed by reoxygenation, catalase's enzymatic prowess is instrumental in attenuating oxidative stress-mediated myocardial injury. By neutralizing hydrogen peroxide, catalase preserves myocardial contractility and mitigates inflammation, thereby mitigating the extent of ischemic damage.[22,23] Moreover, catalase's protective role extends to atherosclerosis, where ROS-mediated lipid peroxidation and endothelial dysfunction drive the progression of vascular lesions. Enhanced catalase expression within endothelial cells counteracts ROS accumulation, preserving endothelial integrity and mitigating the proatherogenic milieu.[24] In addition, it emerges as a pivotal player in combating neurodegeneration, with its expression levels inversely correlated with disease severity in experimental models and clinical studies.[8,14] Within neurons, catalase mitigates ROS-induced oxidative damage to lipids, proteins, and nucleic acids, thereby preserving neuronal viability and function. Furthermore, catalase exerts neuroprotective effects by modulating inflammatory signaling cascades and apoptotic pathways implicated in neurodegeneration.[8,14] By blunting ROS-mediated neuroinflammation and apoptosis, catalase holds promise as a therapeutic target for ameliorating neurodegenerative diseases. Furthermore, catalase, operating as a guardian of pancreatic β-cells and peripheral tissues, counteracts ROS accumulation and preserves insulin sensitivity in the face of metabolic perturbations. In pancreatic β-cells, catalase attenuates oxidative stress-induced apoptosis, thereby safeguarding β-cell mass and insulin secretion capacity.[25] Conversely, diminished catalase activity exacerbates β-cell dysfunction and accelerates the progression of diabetes mellitus.[25,26] Moreover, catalase's protective effects extend beyond pancreatic β-cells to peripheral tissues affected by diabetic complications, including the kidneys, eyes, and blood vessels. By mitigating ROS-mediated tissue damage and inflammation, catalase holds promise as a therapeutic avenue for mitigating diabetic complications and preserving overall metabolic health.[25,26] Importantly, catalase, paradoxically implicated in both tumor suppression and promotion, exerts context-dependent effects on cancer initiation and progression.[1,3] In the early stages of carcinogenesis, catalase's antioxidant properties thwart ROS-induced DNA damage and mutagenesis, thereby suppressing tumor initiation.[27,28] Conversely, in established tumors, catalase's upregulation facilitates cancer cell survival under conditions of oxidative stress, conferring a selective growth advantage and promoting tumor progression.[28] Furthermore, catalase's involvement in redox signaling pathways modulates cancer cell proliferation, angiogenesis, and metastasis, highlighting its multifaceted role in tumor biology. Harnessing catalase's dual nature as both a tumor suppressor and promoter poses intriguing therapeutic implications for cancer treatment, warranting further investigation.[1,3,27,28] Aging, characterized by progressive decline in physiological function and increased susceptibility to age-related diseases, is inexorably linked to the cumulative effects of oxidative stress and cellular damage.[29] Catalase, a key player in the cellular antioxidant defense network, emerges as a crucial determinant of aging trajectory and longevity.[5] Experimental evidence suggests that catalase overexpression extends lifespan and ameliorates age-related pathologies in various model organisms, underscoring its pivotal role in

promoting healthy aging. By mitigating oxidative damage to cellular macromolecules and preserving mitochondrial function, catalase preserves cellular homeostasis and delays the onset of age-related decline.[5] Moreover, catalase's involvement in signaling pathways regulating cellular senescence and apoptosis influences the aging process at the molecular level. Fine-tuning catalase expression and activity holds promise as a therapeutic strategy for promoting healthy aging and extending healthspan in humans.[5]

Gene therapy holds immense promise for delivering therapeutic genes, including catalase, to target tissues and augment endogenous antioxidant defenses. Viral vectors, such as adeno-associated viruses and lentiviruses, serve as efficient vehicles for delivering catalase-encoding genes to target cells, thereby enabling sustained expression and therapeutic benefit.[30] In preclinical models of oxidative stress-related diseases, including ischemic heart disease, Parkinson's disease, and diabetic complications, catalase gene therapy has demonstrated remarkable efficacy in mitigating tissue injury and preserving organ function.[30,31] By conferring long-term protection against oxidative damage, catalase gene therapy offers a transformative approach for treating chronic diseases characterized by dysregulated redox homeostasis. Furthermore, advancements in gene editing technologies, such as CRISPR-Cas9, pave the way for precise genome engineering aimed at modulating endogenous catalase expression. By precisely editing regulatory elements governing catalase expression, investigators can fine-tune antioxidant capacity and mitigate disease progression in a targeted manner.[32] Most importantly, nanoparticle-based delivery systems represent a versatile platform for encapsulating and delivering catalase to target tissues with enhanced precision and efficacy.[33] Engineered nanoparticles, ranging from liposomes to polymeric nanoparticles, offer customizable properties, including size, surface charge, and payload capacity, tailored for specific therapeutic applications.[33,34] These nanoparticle-based delivery systems shield catalase from enzymatic degradation and facilitate its controlled release at the target site, thereby maximizing therapeutic efficacy while minimizing off-target effects. Moreover, surface modifications with targeting ligands enable selective accumulation of catalase-loaded nanoparticles within disease-affected tissues, further enhancing therapeutic outcomes.[33,34] In the realm of regenerative medicine, catalase-loaded nanoparticles hold promise for enhancing tissue repair and regeneration by mitigating oxidative stress-induced damage. By promoting tissue healing and reducing inflammation, catalase-loaded nanoparticles offer a novel approach for treating acute injuries and accelerating wound healing processes.[33,34] In addition, innovative engineering approaches also aimed at enhancing catalase's therapeutic efficacy encompass protein engineering, site-directed mutagenesis, and fusion protein strategies. Rational design of catalase variants with improved stability, catalytic activity, and substrate specificity holds promise for overcoming existing limitations and expanding therapeutic applications.[35-37] Interestingly, directed evolution techniques, coupled with high-throughput screening methodologies, enable the generation of catalase variants with enhanced properties tailored for specific therapeutic contexts.[35-37] By harnessing the power of evolutionary selection, investigators can engineer catalase variants optimized for pharmaceutical production, delivery, and therapeutic efficacy. Moreover, fusion protein strategies, incorporating catalase into multifunctional protein scaffolds, offer a synergistic approach for enhancing therapeutic outcomes. By coupling catalase with targeting moieties, therapeutic peptides, or imaging probes, investigators can confer additional functionalities while augmenting catalase's therapeutic potential.[35-37]

It is also very important to show the navigating challenges and considerations in catalase-based therapies, a primary challenge in catalase-based therapies revolves around ensuring the stability and immunogenicity of the therapeutic agent.[38,39] Native catalase, a heme-containing enzyme, is susceptible to denaturation and degradation under physiological conditions, thereby compromising its therapeutic efficacy. Various strategies have been explored to enhance the stability of catalase, including protein engineering, chemical modifications, and encapsulation within protective matrices.[38,39] Protein engineering approaches, such as site-directed mutagenesis and directed evolution, enable the generation of catalase variants with improved stability profiles and resistance to proteolytic degradation.[38,39] Chemical modifications, such as PEGylation and glycosylation, confer additional stability to catalase by shielding it from enzymatic degradation and immune recognition.[40,41] Moreover, encapsulation of catalase within biocompatible polymers or liposomes offers a protective microenvironment, preserving enzymatic activity and prolonging circulation half-life *in vivo*.[42] Immunogenicity represents another critical consideration in catalase-based therapies, particularly in the context of repeated administrations and long-term treatment regimens. Immune responses directed against catalase or its delivery vehicles can compromise therapeutic efficacy and trigger adverse reactions, necessitating strategies to mitigate immunogenicity.[43] Surface modifications with stealth polymers, such as PEG, reduce the immunogenicity of catalase and prolong its circulation time by evading recognition and clearance by the immune system.[40-42] Moreover, advances in immune tolerance induction and immunomodulatory agents hold promise for mitigating immune responses against exogenous catalase, thereby improving treatment outcomes and patient safety.[43,44] Delivery strategies for efficient targeting are another approach, achieving efficient and targeted delivery of catalase to disease-affected tissues represents a formidable challenge in catalase-based therapies.[40-44] The systemic administration of catalase is hampered by its limited stability, rapid clearance from circulation, and non-specific distribution, necessitating innovative delivery strategies to enhance tissue specificity and therapeutic efficacy.[40-44] Furthermore, nanoparticle-based delivery systems, including liposomes, polymeric nanoparticles, and mesoporous silica nanoparticles, offer a versatile platform

for encapsulating and delivering catalase to target tissues with enhanced precision.[40-44] Surface modifications with targeting ligands, such as antibodies or peptides, enable selective accumulation of catalase-loaded nanoparticles within disease-affected tissues, thereby maximizing therapeutic outcomes while minimizing off-target effects.[40-44] Moreover, advancements in cell-based delivery approaches, including stem cell therapy and engineered cell carriers, facilitate the localized delivery of catalase to specific tissue sites, augmenting its therapeutic efficacy and minimizing systemic side effects.[45,46] Engineered cells expressing catalase can serve as living factories for continuous enzyme production, offering sustained therapeutic benefits and prolonged tissue residence time. Interestingly, understanding the pharmacokinetic and pharmacodynamic properties of catalase is paramount for optimizing dosing regimens, predicting therapeutic outcomes, and ensuring patient safety. The pharmacokinetics of catalase are influenced by various factors, including route of administration, formulation characteristics, and tissue distribution kinetics.[40-46] Intravenous administration of catalase typically results in rapid distribution to tissues with high blood flow, such as the liver, kidneys, and spleen, followed by gradual clearance from circulation.[47] The biodistribution of catalase is further influenced by factors such as molecular size, surface charge, and protein corona formation, which impact tissue penetration and cellular uptake. Pharmacodynamic studies elucidating the dose-response relationships and time-course of catalase activity are essential for optimizing treatment regimens and predicting therapeutic efficacy. While catalase is generally regarded as safe and well-tolerated, certain factors, such as immunogenicity, off-target effects, and enzyme overdose, can precipitate adverse reactions and therapeutic complications.[40-47] Immune responses directed against exogenous catalase or its delivery vehicles can trigger allergic reactions, hypersensitivity responses, and autoimmune phenomena, necessitating careful evaluation of immunogenicity risks in preclinical and clinical studies. Strategies to mitigate immunogenicity, such as immune tolerance induction and immunomodulatory agents, are critical for ensuring patient safety and treatment success.[40-47] Off-target effects resulting from non-specific distribution of catalase or unintended interactions with host tissues can lead to adverse reactions and treatment complications. Minimizing off-target effects through targeted delivery strategies and optimization of dosing regimens is essential for maximizing therapeutic efficacy while minimizing the risk of adverse effects. Enzyme overdose represents another safety concern in catalase-based therapies, particularly in the context of high-dose or prolonged treatment regimens. Excessive catalase activity can disrupt cellular redox balance, interfere with physiological signaling pathways, and precipitate oxidative stress-related damage, highlighting the importance of dose optimization and careful monitoring of treatment response.[40-47]

Recent advances in catalase-based therapies have propelled the field forward, offering innovative solutions to enhance catalase delivery, stability, and activity, while also exploring synergistic combination therapies and translational avenues.[38,48,49] Efficient delivery of catalase to target tissues remains a critical challenge in harnessing its therapeutic potential. Recent advancements in drug delivery technologies offer promising solutions to overcome barriers associated with catalase delivery, including poor stability, limited bioavailability, and non-specific tissue distribution.[50] Nanotechnology has emerged as a frontrunner in catalase delivery, with nanoparticle-based platforms offering enhanced stability, controlled release, and targeted delivery capabilities.[13,33,34,44,45,50] Polymeric nanoparticles, liposomes, and mesoporous silica nanoparticles can encapsulate catalase, protecting it from enzymatic degradation and facilitating its controlled release at the target site.[42,44-47] Moreover, advances in biomaterials and scaffold-based delivery systems enable localized and sustained delivery of catalase to specific tissue sites.[51] Hydrogels, microspheres, and scaffolds engineered with catalase promote tissue regeneration, wound healing, and organ repair by providing a supportive matrix for enzyme release and cellular infiltration.[51,52] Furthermore, cell-based delivery approaches, such as stem cell therapy and engineered cell carriers, offer a novel strategy for delivering catalase to target tissues.[45] Engineered cells expressing catalase serve as living factories for continuous enzyme production, offering sustained therapeutic benefits and prolonged tissue residence time. Recent advancements in protein engineering, chemical modification, and nanotechnology offer innovative approaches to improve catalase stability, activity, and bioavailability.[38,44-50] Protein engineering techniques, such as site-directed mutagenesis and directed evolution, enable the generation of catalase variants with enhanced stability and catalytic efficiency.[37] Rational design of catalase variants with improved resistance to proteolytic degradation and oxidative inactivation holds promise for enhancing therapeutic outcomes. Chemical modifications, including PEGylation, glycosylation, and lipidation, confer additional stability and bioavailability to catalase by shielding it from enzymatic degradation and immune recognition.[40-44] Surface modifications with stealth polymers, such as PEG, reduce immunogenicity and prolong circulation time, enhancing therapeutic efficacy.[40-44] Furthermore, nanotechnology-based approaches, such as enzyme immobilization and encapsulation within protective matrices, offer strategies to enhance catalase stability and activity. Nanostructured materials, such as carbon nanotubes, graphene, and metal-organic frameworks, provide a supportive environment for catalase immobilization, preserving enzymatic activity and facilitating controlled release at the target site.[44-47]

Interestingly, combination therapies integrating catalase with other antioxidants hold promise for synergistically enhancing antioxidant capacity and mitigating oxidative stress-related damage. Recent studies have explored the potential synergistic effects of catalase in combination with other antioxidants, including superoxide dismutase, glutathione peroxidase, and Vitamins C and E.[53] Preclinical

studies have demonstrated enhanced antioxidant efficacy and protective effects against oxidative stress-induced tissue injury with combination therapies targeting multiple ROS-generating pathways. By targeting different ROS species and antioxidant defense mechanisms, combination therapies offer a comprehensive approach for combating oxidative stress-related diseases.[36,53] Moreover, nanoparticle-based delivery systems enable codelivery of catalase with other antioxidants, facilitating synergistic interactions and enhancing therapeutic efficacy. Coencapsulation of catalase and other antioxidants within nanoparticles offers controlled release kinetics and targeted delivery to disease-affected tissues, maximizing therapeutic outcomes while minimizing off-target effects.[54] Most importantly, translational perspectives and clinical trials of catalase-based therapies from bench to bedside require rigorous preclinical evaluation and clinical validation to assess safety, efficacy, and therapeutic potential. Recent advances in translational research have paved the way for clinical trials exploring the feasibility and effectiveness of catalase-based therapies in various disease settings.[55] Clinical trials evaluating the safety and efficacy of catalase-based therapies in oxidative stress-related diseases, including cardiovascular disorders, neurodegenerative diseases, and diabetes mellitus, are underway.[55] These trials aim to elucidate the therapeutic benefits of catalase supplementation, gene therapy, and combination therapies in improving patient outcomes and reducing disease burden. Furthermore, advancements in biomarker discovery and personalized medicine enable the identification of patient populations most likely to benefit from catalase-based therapies. In conclusions, catalase represents a promising therapeutic target for oxidative stress-related diseases, offering multifaceted protective effects against ROS-mediated cellular injury. Catalase ability to scavenge H_2O_2 offers potential in alleviating oxidative damage implicated in the pathogenesis of these ailments. Moreover, catalase-based therapies have the potential to enhance the efficacy of conventional treatments while minimizing associated side effects. Beyond medicine, catalase finds applications in biotechnology and pharmacology, where it is utilized to improve the stability of therapeutic proteins and drugs vulnerable to oxidative degradation. Incorporating catalase in formulations can prolong the shelf life and potency of pharmaceutical products, enhancing their efficacy and safety. Looking forward, the therapeutic potential of catalase continues to evolve. Future directions include the exploration of innovative delivery systems to enhance catalase's bioavailability and targeting specific tissues or cellular compartments. In addition, genetic and protein engineering techniques offer avenues to enhance catalase's enzymatic activity, stability, and specificity for tailored therapeutic applications. Further research and clinical trials are warranted to fully realize the therapeutic potential of catalase in translational medicine.

Competing Interests

The author declares no competing interests.

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